REMARKS/ARGUMENTS

Status of the claims

After entry of this amendment, claims 1, 4,, 7-9, 11-14, 16-22, and 25-30 are pending in this application. New claim 30 has been added. Claims 2-3, 6, 10, 15-17, and 23-24 are canceled without prejudice to future prosecution. Claim 17 was inadvertently listed as withdrawn in the prior office action. New claim 30 is identical to claim 17 as filed. Thus, no new matter has been added by these amendments.

The present invention

The present invention is directed to methods of targeting a compound to a cell using a mutant protective antigen. More particularly, the invention is direct to targeting a compound to a cell over-expressing a plasminogen activator, or a plasminogen activator receptor by administering to the cell (1) a mutant protective antigen protein comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site, wherein the mutant protective antigen is cleaved by a plasminogen activator; and (2) a compound comprising a lethal factor polypeptide comprising a protective antigen binding site; wherein the lethal factor polypeptide binds to cleaved protective antigen and is translocated into the cell, thereby delivering the compound to the cell.

Claim Rejections Under 35 U.S.C. § 103

Claims 1, 4-5, 8, 11-14, 18-22, and 25-30 are rejected as allegedly unpatentable over U.S. Patent No. 5,677,274 (" Leppla *et al.*") in view of U.S. Patent No. 5,817,771 (Bayley *et al.*). For the reasons set forth below, this rejection is overcome.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach

or suggest all the claim limitations. All three elements set forth above must be present in order to establish a *prima facie* case of obviousness.

The cited references alone or in combination do not render the presently claimed invention obvious. As set forth in the Declaration of Dr. Leppla, submitted herewith, one of skill in the art would not have a reasonable expectation of success to practice the claimed invention based on the cited references. As described by Dr. Leppla, Leppla *et al.* discloses that a compound can be delivered to a cell using a binary bacterial toxin (*i.e.*, native anthrax protective antigen or an anthrax protective antigen with an HIV-1 protease cleavage site in place of the native protective antigen cleavage site), but does not disclose or suggest a mutant protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site (*see*, Declaration ¶ 6). Bayley *et al.* merely discloses that a uPA cleavage site can be incorporated into a polypeptide (*i.e.*, an alpha hemolysin polypeptide) that does not contain such a cleavage site (*see*, *id.*). This disclosure does not remedy the deficiency in Leppla *et al.* (*see*, *id.*).

As Dr. Leppla explains, even if one of skill in the art were to combine the disclosures of Leppla *et al.*, and Bayley *et al.* there would be no reasonable expectation of success in being able to practice the presently claimed methods (*see*, Declaration ¶ 7). The present invention is the first demonstration that a mutant protective antigen can be used to deliver a compound to a cell overexpressing a uPA (*see*, Declaration ¶ 7). Binding of a protease to its cleavage site and subsequent proteolytic cleavage is dependent on the three dimensional structure of the proteins (*see*, Declaration ¶ 7). One of skill in the art would not have expected that the uPA overexpressed on the surface of a target cell and the uPA cleavage site on the mutant protective antigen would have come into contact with each other (*see*, Declaration ¶ 7). For example, the uPA cleavage site in the mutant PA might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell (*see*, Declaration ¶ 7). Accordingly, there would be no cleavage of the mutant protective antigen by the uPA or delivery of a compound to the target cell (*see*, Declaration ¶ 7).

Furthermore, the experimental evidence presented in Dr. Leppla's the declaration demonstrates that the claimed methods are surprisingly effective. More specifically, the mutant

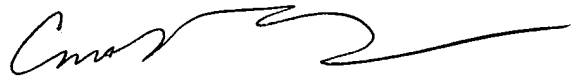
protective antigens of the presently claimed invention are particularly effective for delivering a compound to target cells (*see,* Declaration, ¶ 8). Dr. Leppla describes a series of experiments reported in Rono *et al.*, *Mol Cancer Ther.* 5(1):89-96 (2006) that demonstrate that the claimed mutant protective antigens can deliver a compound to tumors overexpressing uPA when systemically administered to mice bearing tumors that overexpress uPA (*see,* Declaration, ¶ 8). Mutant protective antigens comprising a uPA cleavage site substituted for the native furin cleavage site and compounds comprising a lethal factor polypeptide comprising a protective antigen binding site were systemically administered to mice bearing one of the following types of tumors (*i.e.,* B16 melanoma, T241 fibrosarcoma, or Lewis lung carcinoma), all of which overexpress uPA (*see,* Declaration, ¶ 8). Administration of the mutant protective antigen and lethal factor polypeptides led to significant tumor growth inhibition, demonstrating that the mutant anthrax protective antigens are cleaved by the uPA expressed by the tumor cells and deliver a compound, *i.e.*, lethal factor, to the cells (*see,* Declaration, ¶ 8). The experiments unequivocally demonstrate that the mutant protective antigens of the invention can be used for *in vivo* delivery of a compound to a target cell overexpressing uPA (*see,* Declaration, ¶ 8).

In view of the foregoing, Applicants respectfully submit that the presently claimed invention is nononvious, and thus, patentable over the combination of Leppla *et al.* and Bayley *et al.* Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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